Exp. Pathol. 1989; 37: 119–127
VEB Gustav Fischer Verlag Jena

Paper

NOTICE
This material may be protected by copyright law (Title ...

Quantitative risk approaches for formaldehyde

By C. T. Howlett, R. Mathias and S. Friess

Address for correspondence: Dr. C. T. Howlett, Jr., Georgia-Pacific Corporation, 1875 Eye Street, N.W., Washington, D.C. 20006, USA

Key words: formaldehyde, inhalation; risk methodology; goodness-of-fit test; formaldehyde intake, annual; linearized multistage model

Summary

Formaldehyde presents unique data that highlight significant issues in the extrapolation of animal studies to human risk assessments. Formaldehyde causes rare nasal cancer in rats at 15 ppm, but not at lower levels of 2 ppm and 0.5 ppm in the range of human exposures. Mice and hamster studies even at high levels have results similar to low dose rats. Higginson et al. reviewed the human epidemiology studies and concluded that no excess cancer risk was observed; and if a risk exists, it is very low. Formaldehyde is a natural metabolite – the human body turns over 51 g/day. Cells, therefore, have detoxification and other defence mechanisms to formaldehyde. Recent CIIT biomechanism results elucidate these factors. These data raise two issues: First, the appropriateness of linear quantitative risk methodology given the non-linear nature of the biological data. Either a non-linear (threshold) statistical model or NOEL approach are appropriate risk assessment techniques for formaldehyde. Second, the rare nasal cancer observed in rats also occurs in control animals. A comparison of relative risk between background and low formaldehyde exposures has been calculated for both groups. Non-linear (MLE) 5 stage multistage models estimate 0 per million risk from both background and 1 ppm of formaldehyde exposure. Linear or upperbound (95%) estimates are 7,200/million from background and 5,000/million from 1 ppm formaldehyde. These estimates have a significant impact on formaldehyde regulatory programs for warning labels and "safe" exposure levels.

Formaldehyde is a simple one carbon molecule. Formaldehyde is used in industry, primarily for resins and adhesives and in intermediate steps to manufacture plastics. The largest environmental sources result from the combustion of fossil fuels (7).

Results from the several chronic inhalation studies of rats demonstrate positive responses of squamous cell carcinoma at high dose exposure levels (14.2–15.0 ppm). No positive responses occur at low dose exposures (0.3–2.0 ppm) (6, 1, 13). At intermediate exposures (5.6 ppm) in the CIIT study, a nonstatistically significant response was reported (table 1).

Studies with varying exposures in mice and a single exposure in hamsters demonstrated no significant carcinogenic response. The positive squamous cell carcinoma response in rats was common to both Fisher-344 and Sprague-Dawley rats used in these studies.

The results of the inhalation studies in rats demonstrate a very steep but non-linear dose response curve (11, 12). These data have been modeled using the logit, probit, and multi-stage models. The logit, probit and 4- and 5-stage multi-stage models have acceptable goodness-of-fit values (table 2). The maximum likelihood estimates of risk for theses models reflect the markedly non-linear response observed in these laboratory studies (fig. 1).

PM3006451645

Source: https://www.industrydocuments.ucsf.edu/docs/nkxj0001

Table 1. Experimental data – rats.

Concentration (ppm)	Responses/total
0	0/461
.3	0/32
2.0	0/268
5.6	2/235
14.2	39/100
14.3	103/232
15.0	14/32

Table 2. Results of the goodness-of-fit test.

	Rat Data
Logit (1)	.89
Logit (2)	.97
Logit (3)	.94
Probit (1)	.94
Multistage (1)	<.001
Multistage (2)	<.005
Multistage (3)	.48
Multistage (4)	.97
Multistage (5)	.94
Multistage (6)	.39
Multistage (7)	<.005

Table 3. Comparison of intake of formaldehyde from various sources.

	mg Formaldehyde Intake	mg Formaldehyde from Metabolism	
EPA Unit Risk Annual Total Inhalation of 70 kg Man	7.30		
EPA 10^{-6} Risk Annual Total Inhalation	.562		
Whole Apple (single unit)	2.24		
Tomato (5) (single unit)	.75		
Chicken (6) (single serving)	.46		
Cola Soft Drink (7), (8)	3.00	20.00	
Coffee (9), (10), (11)	.720	30.00	
Normal Metabolism (70 kg)			51 g

Formaldehyde is unique, among commercial chemicals subjected to toxicity testing because it is a natural human body metabolite. Formaldehyde is an essential metabolic intermediate necessary to sustain life itself. Formaldehyde also occurs naturally in a wide variety of animal and vegetable

PM3006451646

Source: https://www.industrydocuments.ucsf.edu/docs/nkxj0001

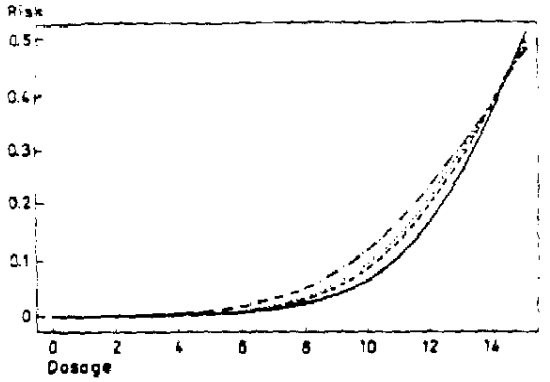

Fig. 1. Maximum likelihood estimates for rat data.

——— Logit maximum likelihood estimate, ····· Probit maximum likelihood estimate. – · – · – Multistage (4) maximum likelihood estimate. – – – – – – Multistage (5) maximum likelihood estimate

materials and is metabolized from caffeine present in coffee and cola soft drinks (*table* 3). IMBUS estimates the range varies considerably from 0.46 mg of uptake from chicken to 30 mg metabolized from caffeine in coffee (5). Over 51 g are produced daily by normal body metabolism (2).

These factors are important because human cells encounter formaldehyde daily and are able to metabolize or otherwise defend themselves against the potential toxic properties by natural defence mechanisms. EPA has calculated a human reference dose from the rat data for a one in a million risk level to be 0.562 mg/year of formaldehyde or 7.30 mg/year for a 70 kg person (table 3). EPA's reference dose is derived from the 5-state multi-stage model and the linearized upper 95% confidence limit (UCL) or upper bound (UB) limit.

HIGGENSON and an expert panel reviewed the epidemiology literature and concluded no human cancers could be attributed to formaldehyde exposure. The principal conclusions from this review are that for no malignancy in man there is convincing evidence of a relationship with formaldehyde exposure and furthermore, that if a relationship does exist, the excess risk, in absolute terms, must be small. (9) Additional toxicity testing results on monkeys is also being reported which assists in better understanding species differences between obligate nose breathers such as rats and man. (10)

Formaldehyde is ubiquitous in the environment. It is present in conventinal homes from construction materials and other consumer products brought into the home. It is present in outdoor ambient air primarily as a result of the by-product of combustion of gasoline. It has also been measured in rural areas and undeveloped atmospheres such as the Amazon basin and Antarctica. Formaldehyde is even present in nominally clean air commonly used in toxicology studies (5). Each of these environmental exposures including Antarctica, the Amazon and even a clean atmosphere has a risk factor that exceeds the 1×10^{-6} factor derived from the upper 95% confidence limit of the linearized multi-stage model (table 4). EPA has also calculated both the upper bound (UB) and the maximum likelihood estimates (MLE) of risk for 2 home residencies and 2 occupational exposure situations (16), (table 5). Fig. 2 presents the data in table 5 in graphic form.

Using the risk factor of 1×10^{-6} as the virtually safe dose (VSD), it is quite evident that as the level of exposure decreases the uncertainty of the risk potency factor increases. The differences between the MLE and the 95% upper bound or the UB increases at an increasing rate as exposure

PM3006451647

Source: https://www.industrydocuments.ucsf.edu/docs/nkxj0001

Table 4. Comparison of annual formaldehyde intake from various sources.

	Annual Inhalation ug/kg	Ratio to EPA Unit Risk Exposure	Ratio to Virtually Safe dose
EPA Unit Risk Based upon .00082 ppm	104.28	1	13
Virtually Safe Dose 10^{-6} Risk .000063 ppm	8.03	.077	1
Conventional Home Dwellers Based upon .07 ppm	8759	89	1090
Urban Dwellers Based upon 0.04 ppm (3)	500.57	48	62
Amazon Basin** Based upon .002 ppm (4)	250.28	2.4	31
Antarctica*** Based upon .002 ppm (5)	250.28	2.4	31
Mobile Home Based upon .072 ppm (2)	9010.29	86.4	1122
Clean Atmosphere (3) Based upon .0004 ppm	50.05	0.48	6.2

* Assumes 24 h per day in environment, and 70 kg average adult inhalation of 20 m^3 of air per day.
** Range of total aldehydes reported .001 – .006. Geometrical mean = .004 – Assumes 1/2 (.002) is formaldehyde.
*** Range of total aldehydes report .005 – .010. Geometrical mean = .004 – Assumes 1/2 (.002) is formaldehyde.

levels decrease. At the old OSHA occupational standard of 3 ppm, the difference between the MLE unit risk and the UB unit risk was apparently 10^{-1}. At the conventional home exposure level of 0.07 ppm, the risk differential is 10^{-7}, between the MLE and the UB values. As exposure levels decrease, the difference factor between modeled MLE estimate and the UB values increases.

It is not surprising that the result of statistical modeling of biological data from animal studies that have markedly non-linear responses display this divergence (4). 2, 3, 7, 8-TCDD, methylene chloride and sodium saccharin exhibit this same result (15). A traditional toxicological approach for determining safe exposure levels is to use the no-observed-effect level (NOEL) from chronic studies and apply a safety factor (10 or 100 fold) consistent with the severity of the toxic effect under consideration. MUNRO completed a biological risk assessment and concluded that for chronic effects, a no-observed adverse effect level (NOEL) for humans to be at 1 ppm exposure (2).

The 95% upper bound risk estimate represents a differential factor over the MLE unit of risk. The previous examples demonstrate that biostatistical modeling of non-linear animal response data generates such differential factors between the UB and MLE on the order of 10,000,000 fold.

PM3006451648

Source: https://www.industrydocuments.ucsf.edu/docs/nkxj0001

Table 5. Estimated risks based on squamous cell carcinoma. Data from CIIT study. Population risks (number of excess tumors) appear in parentheses below individual rik estimates. (Reprinted from EPA table 7–2 from reference 7).

Category	Population	Exposure	MLE Estimate of Risk	Upper Bound Estimate of Risk
Mobile Home Residents	7,800,000*			
Based on current monitoring data		0.10 ppm (112 h/wk for 10 yrs)	2×10^{-10} [B1]** (< 1)	1.5×10^{-4} [B1]** (1,170)
Manufacturers of Apparel	777,000			
Personal Sample		0.64 ppm (36 h/wk for 40 yrs)	6×10^{-7} [B1] (< 1)	1×10^{-3} [B1] (777)
NIOSH Data		0.17 ppm (36 h/wk for 40 yrs)	4×10^{-9} [B1] (< 1)	3×10^{-4} [B1] (233)
Conventional Home Residents	6,310,000*	0.07 ppm (112 h/wk for 10 yrs)	6×10^{-11} [B1] (< 1)	1×10^{-4} [B1] (630)
Unit Risk		1 $\mu g/m^3$ — 0.000.83 ppm (for 70 yrs)		1.3×10^{-5} [B1]
Virtually Safe Dose (10^{-6} Risk)		0.077 $\mu g/m^3$ 0.000.063 ppm		1×10^{-6}***

* Population estimates are based on anticipated additions to the housing stock over the next 10 years as estimated by SCHWEER (1987).

** Classification under EPA's Guidelines for Carcinogen Risk Assessment — [B1] = Probable Human Carcinogen.

*** Authors linear extrapolation from Unit Risk.

The linearized multi-stage model UB estimate is based on a "policy assumption" that any exposure, even a molecule, presents a potential excess risk. This risk is additive to the background risk. Similarly the MLE unit risk factor is also additive to the background risk. However, because the safety factor represented by the difference between the MLE and UB increases as exposures get smaller, the question arises as to whether a prudent safety factor is being greatly overestimated.

The increasing difference between the UB and MLE at lower exposure levels reflects the uncertainty of low dose extrapolations from high dose animal experiments. In addition, adjustments should be made for differences between administered dose to test animals and the delivered dose to target cells. Differences between species where the toxicological end points differ between species also increase the uncertainty and account, in part, for the divergence between the risk estimates.

Because formaldehyde is a natural human metabolite and is ubiquitous in the environment, the policy assumption that exposure to a single molecule of formaldehyde carries an additional unit of risk is overly conservative. As an alternative to this policy approach, use of the background unit of risk from which to derive a more reasonable safety factor that is also consistent with traditional safety factor approaches is described. An alternative approach to providing a safety factor beyond the most likely estimate of risk is prudent and worthwhile.

The National Toxicology Program (NTP) has generated information on background incidence of squamous cell carcinoma of the nasal turbinate in the control rats used in federal NTP chronic inhalation studies (8, 9, 16). This information is combined for both Sprague-Dawley and Fischer-

PM3006451649

Source: https://www.industrydocuments.ucsf.edu/docs/nkxj0001

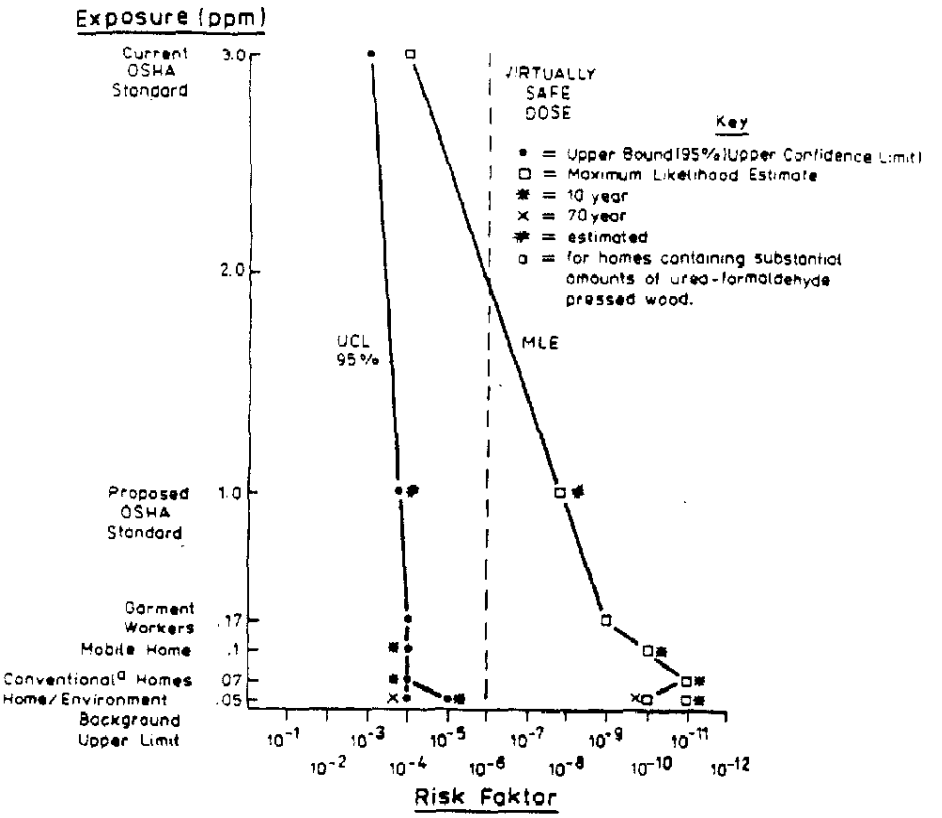

Fig. 2. EPA formaldehyde risk assessment.

Table 6. Experimental data – all studies
Control rats – squamous cell carcinoma.
1 in 3,000 animals.
Source: National Toxicology Program, 1985.

344 rats. NTP reports that this type of cancer has a background incidence rate of 1 in 3,000 animals (table 6). The 3 chronic inhalation studies involving formaldehyde had a total number of 461 control animals from both rat species, so it is not altogether unexpected that the controls in these studies did not exhibit this positive response. Using the combined control data and the combined exposure data of table 1 for the 2 strains of rats, modeling by the MLE and the 95 % UB procedure yields values for background and dose-related increments of risk of nasal cancer. The results are summarized in table 7. From the table it is seen that the MLE background risk value is 0×10^{-6}. Further, for animals exposed at 1 ppm, the incremental risk due to this level of exposure is evaluated as zero by the MLE procedure and $5{,}000 \times 10^{-6}$ by the 95% UB method. Curiously, the dose-related *increment* of risk at 1 ppm by the UB method is even smaller than the background (zero dose) risk evaluated in the same modeling process (i.e. $7{,}500 \times 10^{-6}$).

This modeling process by MLE and UB procedures can be extended to estimates of background and formaldehyde dose-related increments of cancer risk due to workplace exposure. The formaldehyde risk is in addition to background.

PM3006451650

Source: https://www.industrydocuments.ucsf.edu/docs/nkxj0001

Table 7. Modeled results via the 5 stage linearized multistage model.

	MLE (per million)	95% UCB
1.0 ppm Formaldehyde	0	5,000
Background Risk	0	7,200
0.5 ppm Formaldehyde	0	2,500
Background Risk	0	7,200
0.1 ppm Formaldehyde	0	500
Background Risk	0	7,200

Table 8. LMS – comparative risks to fractions of background risk.

	Background	UCB	MLE
2.0 ppm	7,200	10,000	1
1.44 ppm	7,200	7,200	0
1.2 ppm	7,200	720*	0
1.0 ppm	7,200	5,000	0
0.72 ppm	7,200	3,600	0
0.14 ppm	7,200	720	0

In a 2 ppm workplace exposure based on a 40 h/week, 40 year lifetime exposure, MATHIAS modeled the MLE risk increment is 1×10^{-6} and the UB estimtate is $10,000 \times 10^{-6}$. The new U.S. workplace exposure standard of 1 ppm, yields a MLE risk increment of 0×10^{-6} and an UB increment estimate of $5,000 \times 10^{-6}$ shown in table 8.

Most engineering designs use safety factors of 2 or 3 fold. Bridges or buildings are not designed with a million fold safety factor. This provides a useful benchmark in analyzing the relevant safety factors for potential toxicity. In the case of formaldehyde, as exposure decreases, the relevant safety factor, or the ratio of the MLE to the 95% UB risk increments increases; the relative differential factor is not 2 or 3-fold but greater than a million at typically encountered human exposure levels. For chemicals that exhibit a more linear response in chronic lifetime bioassays, the 95% UB risk value normally remains at a 2 to 3-fold difference from the MLE estimate throughout the exposure range. This anomaly of a greater divergence of the MLE and the UB at lower and lower exposures occurs only with non-linear response data from bioassays.

We investigated a modification of the UB curve by its background rate as a means of minimizing this differential. The modification that we propose is to use the background rate for the UB method as the differential modifying factor. In table 8 we note that at the lower dose levels, the difference between the adjusted UB and the MLE method is significantly smaller compared with the differences between unadjusted UB and MLE methods.

In the UB and the MLE unmodified at low doses the difference is in the order of 10^{-7}. In the modified curve Us compared to MLE this difference is reduced to a very much smaller number therefore reducing the variance of the modeling drastically and reasonably accommodating the background at zero dose which the modeling demands. The modified UCB dose corresponding to 1×10^{-6} risk increment will be about 1.44 ppm.

In table 9, 3 methods of determining acceptable exposure levels are summarized, which are the biologically based NOEL, a modeled MLE at 1×10^{-6} risk increment, and a modified UB approach. The 3 methods do not have a large variance in their net result with respect to a safe chronic exposure level. These 3 alternate methodologies for generating acceptable levels of risk exposure

PM3006451651

Source: https://www.industrydocuments.ucsf.edu/docs/nkxj0001

Table 9. Alternative approaches to acceptable levels of risk.

NOEL/ Safety Factor*/	MLE Dose Corresponding to 1×10^{-6} Risk Increment	Modified UB Dose Corresponding to 1×10^{-6} Risk Increment	Unmodified UB – No Correction for Background
1.0 ppm	2.0 ppm	1.44 ppm	0.000,063 ppm

*/ CanTox – NOEL across various species

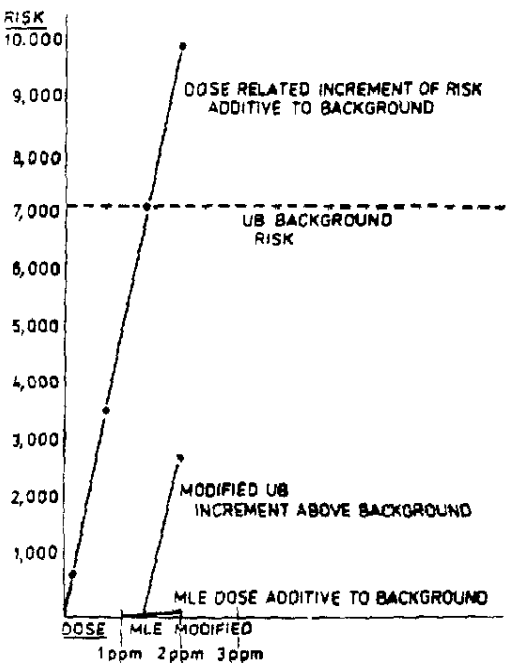

Fig. 3. Dose related increment of risk.

levels for inhaled formaldehyde that are remarkably consistent. The variance is quite small, around a mean of about 1.5 ppm. A comparison of these 3 approaches with the unmodified UB, i.e. unmodified with respect to correction for background, the level is far below the other 3 levels. There is 23,000 fold difference between them.

This approach of utilizing background risk for both the establishment of permissible exposure limits and the determination of the exposure levels for the purposes of providing hazard assessment information and warning labels should be useful. Providing useful information to potentially exposed occupational or environmental populations provides meaningful thresholds and practical benchmarks for these requirements.

Formaldehyde has a markedly non-linear response in animal bioassays, the establishment of safe exposure limits at the unmodified upper 95% confidence limit sets the acceptable additional risk level of 1×10^{-6}. In the modified method, correcting for the background rate of $7,200 \times 10^{-6}$, the dose is 1.44 ppm. This approach is comparable to the value derived from a purely biologically derived risk assessment for chronic inhalation of formaldehyde.

PM3006451652

Source: https://www.industrydocuments.ucsf.edu/docs/nkxj0001

Biostatisticians are advancing the techniques to model non-linear biological data through pharmacokinetic and pharmacodynamic models. These approaches are often times limited because of the lack of data on the relevant biomechanisms. In the interim, while research and progress is made in further refining these more sophisticated approaches to risk assessment, the use of background risks as a differential correction factor for establishing regulatory threshold levels appear to be reasonable and prudent.

References

1. Albert, R. E., Sellakumar, A. R., Laskin, S., Kuschner, M., Nelson, N., Snyder, C. S.: Gaseous formaldehyde and hydrogen chloride induction of nasal cancer in the rat. J. Natl. Cancer Inst. 1982; **68** (4): 596–603.
2. CanTox, Inc.: Biological risk assessment of the potential carcinogenesis from exposure to airborne formaldehyde. CanTox, Inc., Ontario, Canada 1988.
3. Casanova, M., Heck, H., d'A., Steinhagen, W. H., Everitt, J. I., Morgan, K. T., Popp, J. A.: Species and concentration dependence of DNA-protein crosslink (DPX) formation by formaldehyde (HCHO) in Rhesus monkeys and F-344 rats. Toxicologist (in pres).
4. Csorgo, M., Dawson, D. A., Rao, J. N. K., Saleh, A. K. (eds.): Statistics and related topics: proceedings of the international symposium on statistics and related topics. Department of Mathematics and Statistics, Carleton University, Ottawa, Canada 1981.
5. Imbus, H. R.: A review of regulatory risk assessment with formaldehyde as an example. Regul. Toxicol. Pharmacol. 1988; **8**: 356–366.
6. Kerns, W. D., Pavkov, K. L., Donofrio, K. J., Swenberg, J. A.: Carcinogenicity of formaldehyde in rats and mice after longterm inhalation exposure. Cancer Res. 1983; **43**: 4382–4392.
7. National Academy of Sciences (NAS): Formaldehyde and other aldehydes. Committee on Aldehydes and Board on Toxicology and Environmental Health Hazards, NAS. National Academy Press, Washington, D.C. 1981.
8. National Toxicology Program: Technical report series: 1,2-di-bromoethane. NTP-TR 210. 1982a.
9. National Toxicology Program: Technical report series: 1,2-di-bromo-3-chloropropane. NTP-TR 206. 1982b.
10. National Toxicology Program: Technical report series: propylene oxide. NTP-TR 267. 1985.
11. Starr, T. B.: Quantitative cancer risk estimation for formaldehyde. Nasal carcinogenesis in rodents: relevance to human risk. Pudec Publishers, The Netherlands (in press).
12. – Gibson, J. E.: The mechanistic toxicology of formaldehyde and its implications for quantitative risk estimation. Ann. Rev. Pharmacol. Toxicol. 1985; **25**: 745–767.
13. Tobe, M., Kaneko, T., Uchida, Y., Kamata, E., Ogawa, Y., Ikeda, Y., Saito, M.: Studies of the inhalation toxicity of formaldehyde. National Sanitary and Medical Laboratory Service, Toxicity Department of the Organism Safety Research Center, Japan 1985.
14. Universities Associated for Research and Education in Pathology Inc.: Epidemiology of chronic exposure to formaldehyde. Ad Hoc Panel on Health Aspects of Formaldehyde, UAREP, Bethesda, Maryland 1987.
15. U.S. Environmental Protection Agency (EPA): Health assessment document for dichloromethane (methylene chloride). Office of Health and Environmental Assessment, EPA, Washington, D.C. 1985.
16. U.S. Environmental Protection Agency (EPA): Assessment of health risks to garment workers and certain home residents from exposure to formaldehyde. Office of Pesticides and Toxic Substances, EPA, Washington, D.C. 1987.

PM3006451653

Source: https://www.industrydocuments.ucsf.edu/docs/nkxj0001